USDA United States Department of Agriculture

Cooperative State Research, Education, and Extension Service

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Dockets Management Branch
(HFA-305)
US Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

3964 '97 SEP -5 P1:41

Dear Sir:

This letter is in response to your "Request for Comments on Development of Options to Encourage Animal Drug Approvals for Minor Species and for Minor Uses" as presented in the Federal Register volume 62, no. 120, on Monday, June 23, 1997, pages 33781-33783. The Docket number is 97N-0217.

I am certain the industries certainly welcome your efforts to create proactive, responsive drug clearance programs for minor species or for drugs intended for minor uses in major species. FDA personnel are to be commended for their efforts to attain regulatory credibility. Previously these farmers had to decide whether to break the law with attendant consequences, or save their flock.

I have worked with the North American Gamebird Association on this problem, and previous to this briefly with the old IR-4 program. Other minor species have similar difficulties. Legislative restrictions have prevented reasonable solutions to these real world problems. I will provide ideas generated by previous discussions and then attempt to answer your specific questions. Comments will mostly pertain to gamebird conditions, but these concepts would probably apply to other species.

Problems associated with limited drug availability include drug resistance due to using one or two drugs constantly over a period of time, absence of legal drugs for many species, and drug variation in effectiveness between species and between farms or outbreaks. The problems with confining extra label use of drugs to water administration to gamebirds are several. Gamebirds are often held in very large enclosed outdoor pens which makes it extremely difficult to water medicate. Rainwater serves to compete with water treatments because it is an attractive and natural alternative to the water supply provided by management, which may include specific treatments for disease conditions. Medicator use may be confusing to some producers and may fail to properly proportion the medication. Obtaining access to water medications through a veterinarian may or may not be a problem. For example, given the litiginous character of society today, and regulatory punishment associated with intentional or unintentional misuse of therapeutic products, veterinarians may be hesitant to prescribe extra label uses of otherwise over

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today, and regulatory punishment associated with intentional or unintentional misuse of therapeutic products, veterinarians may be hesitant to prescribe extra label uses of otherwise over the counter drugs for water or feed delivery to major species or other minor species. Prevention programs using medications in the feed is easier, cheaper and more humane than treatment of a disease outbreak. Water medication does have its place, but should not be relied on as the sole source of disease prevention or treatment. Owners of major species have access to feed medication, so why should not the gamebird or other minor species? If a drug is cleared for extra label use in water, why should it not be available in the feed? If the target animal safety and residue clearance and efficacy data or indicators are appropriate for water use, it would seem they should apply to feed use.

Drugs for minor species used in medicated feeds is beyond the scope of the Animal Medicinal Drug Use Clarification Act (AMDUCA). There is no doubt the use of extra label drugs in the feed industry should be allowed due to the high probability of proper control, administration and withdrawal recommendations by feed mill personnel.

The gamebird industry requires sufficient protection for their birds. One estimate of value for the USA industry is $200 million. Using the very conservative multiplier effect of three for the value to local communities, this "minor" species represents over $600 million to our economy. Many producers are in the million-plus bird class, but most are small businesses. An untreated disease will cause tremendous economic hardship on producers, yet few viable alternatives exist today.

I recommend that a different set of rules is appropriate and justified for gamebird and other minor species. While efficacy data is important, extensive trials are not warranted. A single or perhaps duplicate trial should be sufficient to establish correlation with existing data for other poultry species. Peer review articles should be accepted as part of the clearance process. Established gamebird farmers have indicated the absence of a requirement for even minimal efficacy evaluations due to their informal communication networks. However, new producers may not have that advantage, so a cursory evaluation would appear appropriate. Clearance should be pursued for all minor species---because a drug is cleared for one species of gamebirds does not mean others are covered (e.g., Bobwhite quail versus pheasants).

I will now answer specific comments and questions outlined in the Federal Register indicated above.

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Column (C) 1, Line (l) 5-8; Summary

Hopefully, the CVM will be able to do more than issue a report on this subject of legislative and regulatory options to facilitate approvals of new animal drugs for minor species or minor uses for

major species. I suggest specific recommendations be made to facilitate this process as a major component of the report.

Paragraph (P) 2 L2; I. Background
Define "turkey". Does this include pen reared wild turkeys (having proper certification) intended for consumption or release?

P3, L8
...in many... This downplays actual conditions. It would probably be more accurate to say ..."in most"..., or ..."in the overwhelming majority" of cases...

C2, P3, L12-15
Also, the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) only authorized extra label therapeutic use of drugs in the water, not in the feed. This is significant and should have been mentioned.

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B. Creating Additional Statutory Authority:

C1, P1, Question (Q) 1
Efficacy studies should be limited to that sufficient to establish a degree of efficacy--one or two trials should serve as confirmation. Existing data in peer review journals or other professional sources should be able to be substituted for additional trials associated with drug approval applications. Producers are willing to cooperate and conduct supervised trials on their farms. Animal safety determinations should be treated in a similar manner. Human safety associated with consumption of the animal (due to hunting activities or through purchase at a grocery store) would demand experiments be conducted to confirm clearance rates determined for other Avian species, and withdrawal times for each drug in question. Drug clearance rates are potentially much different for different species, but if similar, no additional trials should be necessary after confirmation of existing data is obtained.

Q2
It would seem prudent that no difference be shown between use of a drug in a minor specie, and a minor use of a drug for a major specie. If it is a new use, and there is no existing data to support a conclusion, then at least a one confirmatory trial should be conducted.

Q3 to end
Perhaps I have misinterpreted the question, but I do not follow how a person not in the business can accurately define standards for drug residues (i.e., human safety). The goal for all species and all drug residue standards should be to protect humans from drug residues. Other than an expected consumption rate, I do not understand how or why a particular level should be different for different species or uses. Even then, some people will consume gamebirds at a higher rate,

which means they should be protected. Risk of detrimental effects of consuming a product would ideally be the same for all products.

These questions seem like smoke and mirrors or I do not understand the situation. We really are talking about protecting the public from risks associated with drug residues. Period. If a reduced number of experiments indicate that a certain drug is safe as indicated for the current uses in major species, with the appropriate withdrawal times and dosage rates, then the drug should be approved for the minor use or the minor species.

As I understand the situation, the label approval process will require a legislative fix. The label should provide indications for treatment in the appropriate media (feed, water, injection). The label should indicate the drug has been cleared for use under the NRSP-7 plan (or some other program) and indicate the reduced efficacy and animal health testing standards---this is just truth in labeling, and the farmers really do not care as long as the drug works, and if the cursory trials are not totally accurate regarding relative efficacy, the drug will not stay on the market long. At that time the FDA could also pull the label for that species or under the conditions which result in lack of efficacy or animal health.

I touched on this briefly previously. There is no need for extensive experiments if the species in question is found to be similar to the major species. I do not know the current requirement, nor do I know a lot about the residue depletion protocols, so I cannot say with authority exactly how to conduct these trials. However, one would hope common sense would prevail. The reason for the minor use program is that companies will not spend a lot of money to broaden their market to a species that would have a minor profit potential. The program has to make it appealing to the companies so they will file the NADA's. Use of existing data is probably the first step. A single experiment, or a low number of experiments, to determine a correlation with current data would be the next step. For example, not all coccidiostats are effective in the target species and all gamebird species. Thus depletion rates may also be different. That does not mean a full scale approval must be done. It is possible that there are strain effects within species that create differences in drug depletion rates and efficacy---do we know this is not true? Why do we not demand full scale tests for each strain of broilers (e.g., Ross versus Peterson versus Arbor Acres) or laying hens (e.g., DeKalb versus Hy-line)? The justification for reduced testing for gamebirds would be the same reasoning that we do not need to fully test each strain. If there is uncertainty, then additional tests would be appropriate.

P2
This suggestion appears to be reasonable. There is nothing wrong with having a label reflect such a status.

P3
If the foreign review stood the test of a peer review status in our literature, then yes. How does Congress or FDA currently determine if an approval from a foreign country is acceptable for a drug? The same process could be used. It would seem reasonable to require the minor species

be held to our standard of a single or minimal number of tests to verify this foreign data. If the company held the data, and had reproduced it in major species in the USA to allow sales in the USA, then minor species testing would certainly be only what is necessary for approval.

P4

This assumes the current statutory standard is appropriate. If FDA needs to go externally, then the industry (and Land Grant University personnel working in this area) in question could be asked to assist in the process---remember that most gamebird producers are not wealthy, and their association is primarily educational, without a large monetary reserve. The drug companies are not going to pay for a lot of trials---there has to be a payback. Remember also that the commercial turkey industry is often considered too small a market for drug companies to spend money for clearance of new or crossover drugs. FDA should pay for outside reviews, and keep the requirements to a minimum.

P5

I agree that expert panels or compendia would be a defensible alternative for approvals of drugs for minor species and minor uses. Currently existing company data, peer review articles, unpublished trials by university personnel, and field trial data could be used in this process. Standards should come from the approval process and surveillance data (analysis paid for by FDA; production data could be collected in cooperation with land grant university Extension, and other personnel). FDA could develop expert panels represented by scientists within the federal and state governments and industry. Such a standard or monograph would primarily be for educational purposes but could also serve as a basis for future approvals. The panel could be set up in a manner similar to that used by the National Research Council for development of nutritional standards for various animal species. As for the NRC, the panel members would write reports. Commercial production of minor species in gamebirds is not restricted to pheasants or Bob White quail. Producers also raise Hungarian Partridge, Chukar Partridge, Coturnix quail, ducks, etc. Domestic ducks should also be considered part of a minor species program. I believe there are few or no reciprocal clearances for drug use between gamebird species, and there may be some differences in efficacy (thus clearance and safety?) between these species. This program should be used to aggressively pursue clearance of sufficient drugs for use in all minor species.

C. 2. C. Administrative and Regulatory Changes

It is not clear why a different standard for manufacturing drugs for minor species should be used. The issue is clearance of drugs for minor species---with many drugs now existence for the major species which are not allowed to be used in minor species. This program would be to extend legal utilization of existing stocks. If different manufacturing standards were used, a statement to that effect should be on the label. But again, why should different standards be used? To make the drug cheaper? Better?

As far as I recall, the aquaculture strategy has been primarily to develop new drugs, and to expand existing drug clearances to multiple species. In the gamebird industry, we are primarily extending utilization, and recognize new drugs are not within the bounds of reality unless produced for the major species. The latter should also be cleared for use in minor species. If another program uses concepts adaptable to a situation, it would appear to be beneficial to modify and use them as appropriate. One cannot say if a strategy would be successful, but if so for one species, it would seem to be adaptable to others. One drawback is that not all species commodity representatives are as politically well connected and have as strong a commodity organization as aquaculture. This situation would possibly inhibit investigational new animal drug (INAD) information collection.

D. Creating Incentives

P1
I do not believe companies will invest in these niche markets without some sort of incentive that creates the opportunity for a positive cash flow. They certainly will not if producers assume all the risk by using these products illegally. Incentives are absolutely necessary, but should not be so lucrative as to preclude the eventual benefits of competition after a reasonable time period. Company representatives should provide information regarding the best (for both the farmers and producing company) incentive, or mix of incentives.

P2
As I understand the situation, public master files (PMF's) do not provide patent protection and there is no market exclusivity. This situation requires a legislative fix. I believe this process is an integral part of the NRSP-7 program. Other than this drastically inhibitory situation, I can not provide details regarding use the PMF's. If this situation can be overcome by reasonable legislation, then there does not seem to be any negative associated with PMF use, and it would seem considerable easier to use PMF's. As for any legislative or regulatory negative situations, a preferred administrative procedure would be to correct the problem as soon as it is noted.

P3
I am not a spokesperson for the NAGA, but as far as I can determine, gamebird producers and their primary organization, the North American Gamebird Association (NAGA) can not afford to fund these significant levels of research. The NAGA is an educational organization, and does not collect sufficient dues to support such a project. They could participate in field trials that evaluate the efficacy and safety of drugs in question. If properly supervised, and peer review quality data is obtained, I see no reason a company would not support use pf this type data.

P4
Absolutely. There is no reason to allow animals to suffer or people to risk heavy fines or jail by using an unauthorized route of administering a drug required to relieve a disease condition in their animals. This is particularly true of extra label use being approved for a water route of administration but not for the feed. To many persons in the poultry system, previous Federal

positions were an example of yielding to arbitrary political pressure. The current philosophy of cooperation and attempting to resolve problems that face producers is very welcome.

C. 3 P1

This situation raises several "red flags", but the reason for this response is not clear. Animal rights and protection groups, food safety advocacy groups (not that farmers are not advocates of animal well-being and food safety) may be not-for-profit, and "public interest". I would limit this activity to groups that support the minor species in question and eliminate political positioning by groups that do not have the industry's best interests in mind.

P2

A possible mechanism would be removal of veterinarians from legal liability if a producer uses water medication, or a feed mill mixes medicated feed incorrectly for an extra label use. This assumes the veterinarian provided accurate and clear instructions for that situation.

E. Extending Existing Legal Authority

The extra label use of medicated feeds would be reasonable for species not covered, but approval of these drugs certainly would be the best alternative. I assume the extra label use of reproductive hormones is for therapeutic and not production purposes. As long as the withdrawal times are met, and severe penalties exist and occur for intentional abuse of this system, I find nothing wrong with extending AMDUCA for medicated feeds. Because this is a very complicated issue, possibly does not have the system of controls in place as does the drug industry, and which involves significant societal concerns, I do not have an opinion on the extra label use of hormones.

I apologize for the cursory review, but there was not time to provide more detail. Contact me if any of these points require clarification. My contact information is: USDA/CSREES/PAPPP; MS 2220; 901 D Street, SW, Room 842 Aerospace Center; Washington, DC 20250-2220; Telephone: 202.401.5352; Fax: 202.401.1602; e-mail: rreynnells@reeusda.gov.

Sincerely,

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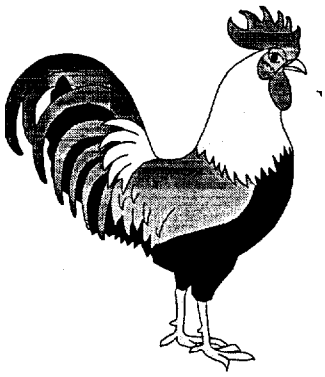

United States Department of Agriculture

Cooperative State Research, Education and Extension Service

Plant and Animal Production, Protection, and Processing

Plant and Animal Production

The enclosed information is sent to you:

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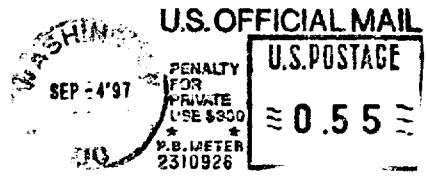

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